Sultan Qaboos University Med J, November 2015, Vol. 15, Iss. 4, pp. e512–516, Epub. 23 Nov 15
Submitted 15 Dec 14
Revisions Req. 9 Mar & 21 May 15; Revisions Recd.23 Mar & 22 May 15
Accepted 22 Jul 15

doi: 10.18295/squmj.2015.15.04.012

CLINICAL & BASIC RESEARCH

Serum Zinc Concentrations in Children with Acute Bloody and Watery Diarrhoea

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مستوى معدن الزنك في مصل دماء الأطفال المصابين بإسهال دَمَويّ أو مائي حاد

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ABSTRACT: ***Objectives:*** The role of zinc in the pathogenesis of diarrhoea is controversial. This study was conducted to compare serum zinc levels in children with acute diarrhoea to those found in healthy children. ***Methods:*** This case-control study was carried out at the Qazvin Children's Hospital in Qazvin, Iran, between July 2012 and January 2013. A total of 60 children with acute diarrhoea (12 children with bloody diarrhoea and 48 children with watery diarrhoea) and 60 healthy children were included. Zinc levels for all subjects were measured using a flame atomic absorption spectrophotometer and data were analysed and compared between groups. ***Results:*** Mean serum zinc levels in the patients with acute bloody diarrhoea, acute watery diarrhoea and the control group were 74.1 ± 23.7 µg/dL, 169.4 ± 62.7 µg/dL and 190.1 ± 18.0 µg/dL, respectively ($P = 0.01$). Hypozincaemia was observed in 50.0% of children with acute bloody diarrhoea and 12.5% of those with acute watery diarrhoea. None of the patients in the control group had hypozincaemia ($P = 0.01$). ***Conclusion:*** Children with acute bloody diarrhoea had significantly reduced serum zinc levels in comparison to healthy children. However, a study with a larger sample size is needed to examine the significance of this trend.

Keywords: Zinc; Diarrhea; Children; Case-Control Study; Iran.

الملخص: الهدف: يعد الدور الذي يلعبه الزنك فيمرض الإسهال أمرا خلافيا. هدفت هذه الدراسة لمقارنة مستوى الزنك في مصل دماء الأطفال المصابين بإسهال دَمَويّ أو مائي حاد مع مستواه عند الأطفال الأصحاء. **الطريقة:** أجريت هذه الدراسة الاستعادية في مستشفى قزوين بإيران بين يوليو 2012 ويناير 2013. وشملت الدراسة 60 طفلا مصابين بإسهال دَمَويّ أو مائي حاد (48 بإسهال مائي و12 بإسهال دموي) و60 طفلا صحيحا. وتم قياس تركيز الزنك في مصل هؤلاء الأطفال عن طريق جهاز مطياف لهب الامتصاص الذري، وحللت النتائج وتمت المقارنة بين المجموعات. **النتائج:** وجد أن متوسط تركيز الزنك في مصل دماء الأطفال المصابين بالإسهال الدموي، وبالإسهال المائي، والأصحاء كان 74.1 ± 23.7 µg/dL و 169.4 ± 62.7 µg/dL و 190.1 ± 18.0 µg/dL، على التوالي ($P = 0.01$). ولوحظ أن 50.0% من الأطفال المصابين بإسهال دَمَويّ حاد، و 12.5% من الأطفال المصابين بإسهال مائي حاد كانوا يعانون من حالة قلة تركيز الزنك في الدم ($P = 0.01$). **الخلاصة:** يعاني الأطفال المصابون بإسهال دموي حاد من نقص معنوي إحصائيا في تركيز الزنك في مصل الدم عند مقارنتهم بالأطفال الأصحاء. غير أنه لمعرفة أهمية هذه النتيجة ودلالتها، يجب القيام بدراسة أخرى بعدد أكبر من العينات.

مفتاح الكلمات: زنك؛ إسهال؛ دراسة حالة ضابطة؛ الأطفال؛ إيران.

Advances in Knowledge

- *The results of the present study confirm the role of zinc in the pathophysiology of acute diarrhoea, particularly for patients with acute bloody diarrhoea.*

Application to Patient Care

- *The findings of this study may inform treatment regimens for children with diarrhoea, as the addition of zinc supplementation may help children recover more rapidly.*

Diarrhoea is defined by the World Health Organization as the excretion of loose or watery stool at least three times within 24 hours.[1] Acute diarrhoea occurs over a few hours or days with a total duration of less than 14 days. It is divided into two types: watery and bloody diarrhoea (dysentery). The main causes of acute diarrhoea include rotavirus, enteroinvasive *Escherichia coli*, *Shigella* and *Salmonella*.[1–3] Diarrhoea is a common condition in children. Based on available data, 2.5 billion diarrhoea cases occur per year among children under five years of age in developing countries.[4] More than 80% of these cases are observed in Asia and Africa, where the incidence of diarrhoea

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is 3.6 episodes annually per child.[1,3,4] Diarrhoea is a significant cause of child mortality worldwide, particularly in developing countries; Boschi-Pinto *et al.* estimated that approximately 1.8 million deaths each year are diarrhoea-related, with most of these deaths occurring in children under five years old.[5]

Micronutrient deficiency is still a notable cause of mortality among patients with diarrhoea despite the introduction of oral rehydration salts (ORS).[6–12] Furthermore, micronutrient deficiency is known to exacerbate diarrhoea and delay recovery time, causing the condition to become chronic.[6–12] Zinc is one of the most important micronutrients and is crucial for free radical detoxification, antioxidant defence and immune system function in humans.[13,14] Zinc levels have been found to be reduced in patients with acute diarrhoea.[6,15] Despite these findings, there is disagreement regarding the efficacy of zinc supplementation for children with acute diarrhoea. Some studies have reported that zinc supplementation accelerates recovery and reduces the duration and severity of diarrhoea, consequently reducing mortality;[16–18] however, other studies do not support these findings.[19–23] Due to this controversy and the high prevalence of acute diarrhoea in Iranian children, this study was conducted to determine serum zinc levels in children with acute diarrhoea in Qazvin, Iran.

Methods

This case-control study was carried out at the Qazvin Children's Hospital in Qazvin between July 2012 and January 2013. Inpatients ≤5 years old who were admitted to the Emergency or Paediatric wards of the Qazvin Children's Hospital due to severe/acute diarrhoea, diarrhoea with vomiting and/or a fever during the study period were included. Acute diarrhoea was defined as the excretion of loose or watery stools at least three times within 24 hours, developing over a few hours or days and lasting fewer than 14 days.[1] Patients with chronic diarrhoea lasting more than 14 days and occurring in conjunction with other underlying diseases such as malnutrition, diabetes, urinary tract infections, septicaemia, pneumonia and other skin or metabolic diseases were excluded from the study. Group matching was used to select the control group from healthy children who were referred to the health centre of the same hospital for evaluation of their growth. Children in both groups resided in Qazvin Province and were similar in age and gender.

The sample size was calculated according to the following formula:[24]

$$n = \frac{2(z_{[1-\frac{\alpha}{2}]}+z_{[1-\beta]})^2\sigma^2}{(\mu_1-\mu_2)^2}$$

Where α is 0.05, $1-\alpha/2$ is 0.95, β is 0.2, $1-\beta^2$ is 0.8, σ is 8, μ_1 is 79 μg/dL and μ_2 is 83 μg/dL. Consecutive sampling was used until the desired sample size was reached. A total of 60 children with acute diarrhoea and 60 healthy children were included. The children with acute diarrhoea were divided into watery (n = 48) and bloody (n = 12) diarrhoea groups. The children with acute diarrhoea were also subdivided according to dehydration severity into mild (<5%), moderate (5–10%) and severe (>10%) groups.[3,25]

The demographic information and symptoms of all subjects were recorded. Prior to beginning treatment for diarrhoea, blood samples from the experimental group were analysed to measure erythrocyte sedimentation rates and C-reactive protein levels and white blood cell, neutrophil and platelet counts. All tests were performed in the Laboratory Department of Qazvin Children's Hospital using standard methods. To measure serum zinc levels, 3 mL of blood were drawn from the peripheral vessels of all of the children. Serum was obtained by centrifugation at 3,000 revolutions per minute for five minutes at 4 °C. The serum was then poured into acid-washed tubes and stored in a freezer at -20 °C until the serum zinc assays were completed. Serum zinc levels were then measured using a flame atomic absorption spectrophotometer (GBC Scientific Equipment Pty Ltd, Braeside, Victoria, Australia) in the Biochemistry Department of Qazvin University of Medical Sciences in Qazvin. Levels of 70–120 μg/dL were considered to indicate a normal range and levels of less than 70 μg/dL were considered to indicate hypozincaemia.[26]

Data were entered into the Statistical Package for the Social Sciences (SPSS), Version 16 (IBM Corp., Chicago, Illinois, USA). The results were analysed using Chi-squared and Tukey's post *hoc* tests and Spearman's rank correlation coefficient and Pearson's correlation coefficient analyses. A value of P <0.05 was considered statistically significant.

This study was approved by the Ethics Committee of the Research Department at the Qazvin University of Medical Sciences (project #303). The parents of all subjects gave written informed consent for their inclusion in the study.

Table 1: Demographic data of children with acute diarrhoea in comparison to an age- and gender- matched control group in Qazvin, Iran (N = 120)

Variable	Acute diarrhoea group (n = 60)	Control group (n = 60)	*P* value
Male-to-female ratio*	37:23	38:22	0.99
Mean age in months ± SD†	28.8 ± 15.2	30.1 ± 15.5	0.65
Mean weight in kg ± SD†	12.3 ± 3.1	12.8 ± 2.9	0.80
Height in cm ± SD†	88.9 ± 12.1	89.3 ± 11.6	0.90
Median head circumference in cm ± IQR‡	46 ± 2.0	46 ± 3.0	0.73

SD = standard deviation; IQR = interquartile range.

**Calculated using the Chi-squared test. †Calculated using the Student's t-test. ‡Calculated using the Mann-Whitney U-test.*

Table 2: Characteristics of diarrhoeal illness among children with acute diarrhoea in Qazvin, Iran (N = 60)

Characteristic	n (%)
Type of diarrhoea*	
Watery	48 (80.0)
Bloody	12 (20.0)
Mean frequency ± SD†	6.0 ± 1.5
Mean duration of illness in days ± IQR‡	2.1 ± 1.0
Dehydration severity*§	
Mild	17 (28.3)
Moderate	30 (50.0)
Severe	13 (21.7)
Symptoms	
Fever	48 (80.0)
Vomiting	34 (56.7)
Abdominal pain	21 (35.0)
Lack of appetite	16 (26.7)
Stool culture results	
No growth	32 (53.3)
Pathogenic *Escherichia coli*	15 (25.0)
Shigella	10 (16.7)
Salmonella	3 (5.0)

SD = standard deviation; IQR = interquartile range.

**Calculated using the Chi-squared test. †Calculated using the student's t-test. ‡Calculated using the Mann-Whitney U test. §Dehydration severity was classified into mild (<5%), moderate (5–10%) and severe (>10%) categories.*

Table 3: Mean serum zinc levels and hypozincaemia among children with acute diarrhoea in comparison to an age- and gender- matched control group in Qazvin, Iran (N = 120)

	Acute diarrhoea group		Control group (n = 60)	*P* value
	Bloody (n = 12)	Watery (n = 48)		
Mean zinc ± SD in µg/dL*	74.1 ± 23.7	169.4 ± 62.7	190.1 ± 18.0	0.01
Hypozincaemia,† n (%)‡	6 (50.0)	6 (12.5)	0 (0.0)	0.01

SD = standard deviation.

**Calculated using the Tukey's post hoc test. †Serum zinc levels of <70 µg/dL. ‡Calculated using the Chi-squared test.*

Table 4: Serum zinc levels according to causative organism of bacterial acute diarrhoea among children in Qazvin, Iran (N = 28)

Zinc in µg/dL	Causative organism			*P* value
	Pathogenic *Escherichia coli* (n = 15)	*Shigella* (n = 10)	*Salmonella* (n = 3)	
Minimum	50.0	50.0	155.0	0.01
Maximum	95.0	120.0	180.0	
Mean ± SD	74.0 ± 13.2	74.0 ± 25.0	170.0 ± 13.2	

SD = standard deviation.

Table 5: Correlation between serum zinc levels and inflammatory and non-inflammatory variables among children with acute diarrhoea in Qazvin, Iran (N = 60)

Variables	Serum zinc levels					
	Acute diarrhoea (n = 60)		Acute watery diarrhoea (n = 48)		Acute bloody diarrhoea (n = 12)	
	R	*P* value	R	*P* value	R	*P* value
Inflammatory						
Fever	-0.43	0.01	-0.26	0.06	-0.20	0.40
WBC	-0.68	0.01	-0.52	0.01	-0.24	0.40
Neutrophils	-0.74	0.01	-0.62	0.01	-0.42	0.16
ESR	-0.83	0.01	-0.78	0.01	-0.50	0.06
CRP	-0.82	0.01	-0.75	0.01	-0.27	0.30
Non-inflammatory						
Dehydration severity	0.52	0.01	0.6	0.01	-0.24	0.40
Type of diarrhoea	-0.52	0.01	-	-	-	-
Causative organism	-0.86	0.01	-	-	-	-

WBC = white blood cell count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

Results

A total of 60 children with acute diarrhoea and 60 healthy children were included. There were 37 males (61.7%) and 23 females (38.3%) among the acute diarrhoea group, while the control group had 38 males (63.3%) and 22 females (36.7%). Subjects in the diarrhoea group ranged from 3–60 months old while those in the control group ranged from 3–57 months old. There was no significant difference between the groups in terms of age, gender, weight, height or head circumference (P >0.05) [Table 1].

Diarrhoeal illness characteristics of the patients with acute diarrhoea are shown in Table 2. Of the 60 children with acute diarrhoea, 12 had bloody diarrhoea and 48 had watery diarrhoea. The mean serum zinc levels among those in the acute bloody diarrhoea, acute watery diarrhoea and control groups were 74.1 ± 23.7 µg/dL, 169.4 ± 62.7 µg/dL and 190.1 ± 18.0 µg/dL, respectively (P = 0.01). Hypozincaemia was observed in 50.0% of the children with acute bloody diarrhoea and 12.5% of the children with acute watery diarrhoea. However, none of the children in the control group had hypozincaemia (P = 0.01) [Table 3].

Among the children with acute diarrhoea, 28 were found to have bacterial diarrhoea caused by the following organisms: *E. coli* (n = 15), *Shigella* (n = 10) and *Salmonella* (n = 3). A significant difference was observed in the mean serum zinc levels of these patients (P = 0.01) [Table 4]. Correlations between serum zinc levels and inflammatory and non-inflammatory variables among children with acute diarrhoea is shown in Table 5.

Discussion

Zinc is an essential nutrient for humans and plays an important role in immunological processes and the adequate functioning of many macromolecules. Hypozincaemia can cause various diseases, including acute diarrhoea, by disrupting the defence system and reducing antioxidant activity.[27] Some researchers believe that the administration of zinc to patients with diarrhoea accelerates their recovery by facilitating rapid regeneration of the intestinal epithelium and increasing brush border (apical) enzymes.[18,27] This provides a zinc transporter for enterocytes and enhances the immune response. The result of these pathophysiological changes is the improvement of water and electrolyte absorption, as well as the faster removal of pathogenic organisms from the intestine.[18,27] Although the exact mechanism of zinc in water and electrolyte transportation in the intestine is not clear, this effect may be due to the inhibition of adenosine 3',5'-cyclic monophosphate-induced chloride-dependent fluid secretion in the small intestine.[27]

In the current study, children with acute bloody diarrhoea had significantly lower serum zinc levels in comparison with healthy children. Additionally, hypozincaemia was observed in half of the children with acute bloody diarrhoea and some of those with acute watery diarrhoea while none of the control group had hypozincaemia. This reduction in serum zinc levels may be related to either the excretion of zinc following acute diarrhoea or metabolic reactions against the infections (known as acute phase responses) or both.[15,20,28,29]

Many studies have reported contradictory results on the effect of zinc in the treatment of acute diarrhoea. A study of 3–59-month-old children affected with acute diarrhoea in Bangladesh indicated that the daily administration of 20 mg of zinc reduced the duration and frequency of diarrhoea.[16] Al-Sonboli *et al*. also found that the administration of zinc reduced the duration of diarrhoea among Brazilian children <5 years old.[17] A study by Bahl *et al*. in India revealed that the administration of zinc along with ORS reduced the severity of acute diarrhoea among children between 6–35 months old.[18] In contrast, Patel *et al*. demonstrated that the administration of zinc did not affect the duration of or rate of complications arising from acute diarrhoea among children aged 6–59 months receiving either ORS and zinc or ORS and a placebo.[20] The researchers suggested that the inefficacy of zinc in their study may have been attributable to a low dose of zinc, poor compliance and the failure of the supplements to replenish the zinc loss.[20] Other studies have confirmed these results.[21–23]

The primary limitation of the current study was the failure to measure serum zinc concentrations after patients had completed their course of treatment. Additionally, the sample size was small. As a result, future studies with a larger sample size are recommended to assess the efficacy of zinc supplementation among patients with acute diarrhoea.

Conclusion

The results of this study showed a trend towards reduced serum zinc levels in children with acute bloody diarrhoea as compared with healthy children in a control group. However, a study with a larger sample size is needed to study the significance of this trend and to resolve the on-going controversy regarding the efficacy of zinc supplementation as a treatment option for individuals with acute diarrhoea.

ACKNOWLEDGEMENTS

The researchers would like to thank the participants and their parents for their cooperation in this study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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